Early Neonatal Bilirubin, Hematocrit, and Glucose-6-Phosphate Dehydrogenase Status

WHAT'S KNOWN ON THIS SUBJECT: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an important risk factor for neonatal jaundice in Nigeria. It is associated with severe hyperbilirubinemia among infants exposed to icterogenic agents. Elevated bilirubin levels have occasionally been demonstrated in G6PD-deficient infants without exposure to icterogenic agents.

WHAT THIS STUDY ADDS: Even without exposure to known icterogens, G6PD-deficient infants have a more rapid hematocrit decline and higher bilirubin levels than their G6PD-intermediate and G6PD-normal counterparts throughout the first week of life.

abstract

OBJECTIVE: To document the patterns of bilirubin and hematocrit values among glucose-6-phosphate dehydrogenase (G6PD)-deficient and G6PD-normal Nigerian neonates in the first week of life, in the absence of exposure to known icterogenic agents.

METHODS: The G6PD status of consecutive term and near-term neonates was determined, and their bilirubin levels and hematocrits were monitored during the first week of life. Infants were stratified into G6PD deficient, intermediate, and normal on the basis of the modified Beutler's fluorescent spot test. Means of total serum bilirubin (TSB) and hematocrits of the 3 groups of infants were compared.

RESULTS: The 644 neonates studied comprised 353 (54.8%) boys and 291 (45.2%) girls and 540 (83.9%) term and 104 (16.1%) near-term infants. They consisted of 129 (20.0%) G6PD-deficient, 69 (10.7%) G6PD-intermediate, and 446 (69.3%) G6PD-normal neonates. The G6PD-deficient and G6PD-intermediate infants had higher mean TSB than their G6PD-normal counterparts at birth and throughout the first week of life ($P < .001$). Mean peak TSB levels were 14.1 (9.48), 10.2 (3.8), and 6.9 (3.3) mg/dL for G6PD-deficient, G6PD-intermediate, and G6PD-normal neonates, respectively. Peak TSB was attained on approximately day 4 in all 3 groups, and trends in TSB were similar. Mean hematocrits at birth were similar in the 3 G6PD groups. However, G6PD-deficient and -intermediate infants had higher declines in hematocrit, bilirubin levels, and need for phototherapy than G6PD-normal infants ($P < .001$).

CONCLUSIONS: The G6PD-deficient and G6PD-intermediate neonates had a higher risk of neonatal hyperbilirubinemia and would therefore need greater monitoring in the first week of life, even without exposure to known icterogenic agents. *Pediatrics* 2014;134:e1082–e1088

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KEY WORDS

bilirubin, haematocrit, glucose-6-phosphate dehydrogenase, neonate, nigeria

ABBREVIATIONS

G6PD-deficiency—glucose-6-phosphate dehydrogenase deficiency
Hb—hemoglobin
TSB—total serum bilirubin

Dr Badejoko conceptualized and designed the study including the data collection instrument, supervised the data collection, and drafted the initial manuscript; Professor Owa contributed to the design of the study and reviewed and revised the manuscript; Dr Oseni contributed to the design of the study and critically reviewed the manuscript; Dr Badejoko contributed to study design, supervised the data collection, performed initial analyses, and reviewed and revised the initial manuscript; Professor Fatusi contributed to study design, performed initial analyses, and reviewed and revised the initial manuscript; Professor Adejuyigbe critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is implicated as the major factor associated with the high prevalence of severe neonatal hyperbilirubinemia, acute bilirubin encephalopathy, kernicterus, and cerebral palsy among Nigerian infants.[1–4] In 1 study, G6PD deficiency was identified in up to 62% of infants with kernicterus.[4] Most of those neonates who had G6PD deficiency and kernicterus were admitted from home with a history of inadvertent previous exposure to known icterogenic agents.[5] In contrast, less is known about the pattern of bilirubin in relation to G6PD status per se. Results of a few studies suggest that even in the absence of exposure to icterogenic agents, G6PD deficiency may be associated with higher levels of total serum bilirubin (TSB).[6]

The patterns of hyperbilirubinemia and hematocrits in G6PD-deficient infants who are not exposed to known icterogenic agents compared with G6PD-normal infants has not been well documented in any Nigerian study. In Nigeria, infants are not routinely screened for G6PD deficiency, and the widespread practice of early discharge from the hospital means that many newborns in Nigeria are discharged before jaundice appears, without a baseline risk assessment. In this study, we aimed to determine the prevalence of G6PD deficiency among term and near-term neonates, determine the influence of G6PD status on bilirubin levels and hematocrits in the absence of exposure to known icterogenic agents in the first week after birth, and ascertain the need for treatment. Findings from this study have potential to inform recommendations regarding routine G6PD screening and predischarge risk assessment for significant hyperbilirubinemia in Nigeria.

METHODS

This was a prospective observational study conducted in the labor, postnatal, and neonatal wards of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria, between May and October 2011. The hospital is a major referral center serving the health needs of the urban and rural communities of Osun and the neighboring states of Ondo and Ekiti, southwestern Nigeria. It records an average of 2500 deliveries annually.

The calculated sample size was 110 G6PD-deficient and 440 G6PD-normal infants (ratio 1:4) based on the prevalence rate of jaundice among G6PD-deficient and G6PD-normal infants from a previous study,[6] statistical power of 80% and type 1 error margin of 5%. The study subjects comprised consecutive term and near-term (35–36 weeks)[7] infants delivered in Obafemi Awolowo University Teaching Hospitals Complex. Babies with major congenital anomalies or sepsis and those with moderate or severe birth asphyxia (first minute Apgar score $\leq$5) were excluded from the study. Ethical approval was obtained from the health research and ethics committee of the hospital before commencement of the study, and a written informed consent to participate in the study was obtained from parents of each infant before enrollment in the study.

Relevant information was obtained from each mother before delivery, including sociodemographic and obstetric data. Gestational age was calculated from the mothers' last menstrual period (LMP), and the modified Ballard scoring system[8] was used for near-term infants and those whose mothers were not sure of their LMP. Immediately after delivery of each infant, a cord blood sample was obtained for G6PD assay, hematocrit, ABO/rhesus blood group determination, direct Coomb test, and TSB assay. The G6PD assay was based on the modified Beutler fluorescent spot test,[9] using the G6PD screening test kit no 203A (Trinity Biotech, Dublin, Ireland). The G6PD-normal result of this test at 37°C is equivalent to 10.1 to 18.7 U/g hemoglobin (Hb) by spectrophotometry, G6PD intermediate corresponds to 3.3 to 6.1 U/g Hb, and G6PD deficient is equivalent to $<$1.6U/g Hb.

Measurement of TSB was done using the Neo-Bil Plus neonatal bilirubin analyzer (Das, Palombara Sabina, Italy), and TSB values $>$15 mg/dL were validated at the hospital laboratory where direct and conjugated bilirubin was measured. Hematocrit, direct Coomb test, and blood grouping were performed by using standard procedures.[10] Each infant was weighed in kilograms to the nearest 10 g using an electronic infant scale (Lincoln Medical, Salisbury, England) at birth, 24 hours, and 48 hours after delivery and on days 4 and 8 after delivery. Other investigations that were carried out when indicated included blood culture, full blood count, blood film appearance, random blood sugar, electrolytes and urea, urine culture, and cerebrospinal fluid analysis and culture. Hematocrit and TSB estimations were repeated at about 24 hours, 48 hours, and on days 4 and 8 for all the infants.

Those infants with significant hyperbilirubinemia were admitted and treated with intensive phototherapy (minimum irradiance of 30 μW/cm^2/nm).[11] Intensive phototherapy was commenced at TSB of 12 mg/dL before the fourth day after delivery or 16 mg/dL thereafter, except for infants who were near term or low birth weight, for whom this was individualized. Their bilirubin and hematocrit were monitored every 6 hours according to the unit protocol. Exchange blood transfusion was reserved for infants with TSB $>$25mg/dL or bilirubin $\geq$10 mg/dL per kg body weight, or infants who failed to respond to intensive phototherapy. Other modalities of treatment such as antibiotics and intravenous fluids were administered as necessary.

The results of the G6PD assay, blood group, hematocrit, and TSB were communicated to the mothers before

discharge. Furthermore, the implications of all the results were explained to mothers, who were specifically educated and counseled about G6PD deficiency. Each mother was then given a list of items (icterogenic agents) to avoid in their infants.[5] Included in the list were camphor (*caphura*), all mentholated products such as balms and dusting powder, quinine, sulfonamides or sulfa-containing drugs, and all herbal remedies. The mothers were also advised to return earlier than the next scheduled study follow-up visit if they noticed jaundice or any other problems in their infants. Mothers were typically discharged from the hospital with their infants on the first or second day after a vaginal delivery and between the second and fourth day after an uncomplicated caesarean delivery. Telephone reminders and home visits were deployed appropriately to minimize loss of study subjects to follow-up.

Each subject's data were recorded in an individual study pro forma. The data were then entered into a spreadsheet and analyzed by using SPSS version 13 and Computer Programs for Epidemiologists (PEPI) Version 4.0. Means were compared by using the analysis of variance with Tukey and Tamhane post hoc tests or Student's *t* test as appropriate; proportions were compared by using χ^2. *P* values $<.05$ were accepted as statistically significant.

RESULTS

In all, 691 infants were recruited for this study. Forty-seven of them (7.3%) were lost to follow-up and failed to complete the study, and thus 644 newborns, comprising 353 boys (54.8%) and 291 girls (45.2%) completed the study, for a male-to-female ratio of 1.2:1. There were 540 (83.9%) term infants (estimated gestational age of ≥37 weeks) and 104 (16.1%) near-term infants (estimated gestational age of 35–36 weeks). Their birth weights ranged from 1.28 to 4.50 kg, with a mean of 2.98 (0.58) kg.

One hundred and twenty-nine (20.0%) of the infants were G6PD deficient, giving a prevalence of G6PD deficiency of ~20%. Table 1 shows the distribution of some of the perinatal characteristic features in relation to the G6PD status. There was no statistically significant difference in any of the parameters except gender in relation to G6PD status. The prevalence of G6PD-deficiency was statistically significantly higher in males than females ($P = .01$). The male-to-female ratio of G6PD-deficient infants was 1.6:1, that of the G6PD intermediate was 1:1.5, and that of G6PD normal was 1:1.05. There was also no statistically significant difference in the proportion of infants with ABO incompatibility setup (blood group A or B infant of a blood group O mother) between the 3 groups ($P = .58$), and none of the infants in this study had a positive direct Coomb test.

Table 2 shows the distribution of mean TSB levels of the infants in relation to G6PD status and postnatal age. The 0-hour TSB ranged from 1.0 to 7.5 mg/dL, and the peak TSB ranged from 1.2 to 26.4 mg/dL. The mean total serum bilirubin on each of the days was highest among the G6PD-deficient infants and lowest in the G6PD-normal infants ($P < .001$). The Tukey and Tamhane post hoc tests showed that each of the intergroup differences as was statistically significant ($P < .001$): the G6PD-deficient infants had significantly higher mean TSB values than the G6PD-intermediate infants, who in turn had significantly higher mean TSB than the G6PD-normal infants. The test of linearity also demonstrated a statistically significant linear relationship between the 3 groups ($P < .001$).

Figure 1 shows the distribution of the TSB values in each G6PD group in relation to postnatal age. All 3 groups showed an initial rise in mean TSB from 0 hours to day 4, followed by progressive decline until day 8. Peak levels of TSB were attained at a mean postnatal age of 3.9 days in all the G6PD groups, as shown in Table 2. However, the rate of rise of TSB was greatest in the G6PD-deficient group (0.09 mg/dL/hour), followed by the G6PD-intermediate group (0.07 mg/dL/hour), and the G6PD-normal group had the lowest value (0.04 mg/dL/hour). This was statistically significant ($P < .001$), as shown in Table 2. The ratio of

TABLE 1 Distribution of Some of the Perinatal Characteristic Features in Relation to G6PD Status

Parameter	G6PD Status			*P*
	Deficient (*n* = 129)	Intermediate (*n* = 69)	Normal (*n* = 446)	
Gestational age, mean (SD), wk	38.4 (1.8)	38.3 (2.2)	38.3 (1.8)	.84[a]
Birth wt, mean (SD), kg	3.0 (0.6)	2.9 (0.7)	3.0 (0.6)	.37[a]
1-min Apgar score, mean (SD)	8.7 (1.5)	8.8 (1.4)	8.7 (1.6)	.81[a]
5-min Apgar score, mean (SD)	9.8 (0.5)	9.9 (0.5)	9.9 (0.6)	.91[a]
Age feeding commenced, mean (SD), min	343.3 (573.7)	431.6 (674.7)	329.3 (504.8)	.34[b]
Mode of feeding, *n* (%)[c]				
Breastfeeding	121 (93.8)	67 (97.1)	423 (94.8)	
Formula feeding	3 (2.3)	0 (0)	11 (2.5)	
Mixed feeding	5 (3.9)	2 (2.9)	12 (2.7)	.69[§]
ABO incompatibility setup, *n* (%)[c]				
Present	8 (14.3)	5 (13.5)	46 (18.8)	
Absent	48 (85.7)	32 (86.5)	199 (81.2)	.58[d]
Gender, *n* (%)[e]				
Male	84 (23.8)	31 (8.8)	238 (67.4)	
Female	45 (15.4)	38 (13.1)	208 (71.5)	.01

[a] Analysis of variance.
[b] Kruskal-Wallis.
[c] Figures in parenthesis are percentages of total in each column.
[d] χ^2.
[e] Figures in parenthesis are percentages of total in that row.

TABLE 2 Distribution of Mean TSB Levels in Relation to G6PD Status and Postnatal Age

Time	TSB (mg/dL)						P^a
	G6PD Deficient (n = 129)		G6PD Intermediate (n = 69)		G6PD Normal (n = 446)		
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
0 h (mg/dL)	3.7 (1.1)[b]	1.7–6.7	2.9 (0.8)[c]	1.1–4.9	2.5 (0.8)	1.0–7.5	<.001
24 h (mg/dL)	6.8 (2.0)[b]	2.4–14.7	4.9 (1.8)[c]	1.3–10.2	3.9 (1.7)	1.0–12.5	<.001
48 h (mg/dL)	9.8 (2.9)[b]	2.6–19.4	7.1 (2.7)[c]	2.2–14.3	5.3 (2.6)	1.0–16.4	<.001
Day 4 (mg/dL)	12.6 (3.7)[b]	3.8–26.4	9.7 (3.7)[c]	2.6–25.0	6.7 (3.0)	1.1–15.6	<.001
Day 8 (mg/dL)	8.4 (2.5)[b]	1.3–18.0	6.7 (2.5)[c]	1.4–11.1	4.2 (2.4)	1.0–17.9	<.001
Peak TSB (mg/dL)	14.1 (9.5)[b]	3.8–26.4	10.2 (3.8)[c]	2.6–25.0	6.9 (3.4)	1.2–17.9	<.001
Age at peak (d)	3.9 (1.2)	1.0–8.0	3.9 (1.1)	1.0–8.0	3.9 (0.9)	1.0–8.0	.48
Rate of rise (mg/dL/h)	0.09 (0.04)[b]	0.02- 0.24	0.07 (0.03)[c]	0.00–0.22	0.04 (0.03)	0.01–0.14	<.001

[a] Analysis of variance.

[b] Value for G6DP-deficient infants significantly different from that of G6DP intermediate infants ($P < .001$).

[c] Value for G6DP-intermediate infants significantly different from that of G6DP normal infants ($P < .001$).

mean TSB between G6PD-deficient, -intermediate, and -normal subjects were 1.5:1.2:1 at 0 hours, compared with 2:1.6:1 at the peak (at approximately day 4).

The hematocrits ranged from 32.0% to 70.0% within the first 8 days. Table 3 shows the distribution of mean of hematocrits of the infants in relation to postnatal age and G6PD status. Hematocrits were highest at 0 hours in all the G6PD status groups and lowest on day 8 ($P < .001$). Comparison of the mean difference between 0 hours and day 8 hematocrits in the 3 groups revealed a statistically significant decline in hematocrits from 0 hours to day 8 in all 3 G6PD groups ($P < .001$; not shown). This decline was largest in the G6PD-deficient group and smallest in the G6PD-normal group. The distribution of hematocrit in each G6PD group from 0 hours to day 8 is shown in Fig 2.

Table 4 shows the clinical outcomes such as significant bilirubinemia (TSB ≥12 mg/dL) and phototherapy compared on the basis of G6PD status and gender. There was no significant difference between male and female infants in any of these outcomes across all the G6PD groups. On the whole, a significantly higher proportion of G6PD-deficient infants had hyperbilirubinemia compared with the G6PD-intermediate group (68.2% vs 27.5%; $P < .001$), who in turn also had a significantly higher proportion than the G6PD-normal group (27.5% vs 7.4%; $P < .001$). None of the subjects in the current study had exchange blood transfusion. Seventy-four (57.4%) of the G6PD-deficient infants, 20 (29.0%) of the G6PD-intermediate infants, and 40 (9.0%) of the G6PD-normal infants received phototherapy ($P < .001$). The G6PD-deficient group had the longest mean duration of phototherapy of 2.4 (2.4) days, followed by the G6PD-intermediate group with 1.0 (1.6) days and the G6PD-normal infants 0.4 (1.3) days ($P < .001$). Although most of the infants that had phototherapy commenced on the fourth day after birth, the G6PD-deficient group was observed to have a wider variation of age at commencement of phototherapy ranging from days 1 to 8 compared with the other 2 groups that ranged from days 2 to 5. None of the study subjects had acute bilirubin encephalopathy or died.

DISCUSSION

Neonatal jaundice is a major cause of neonatal morbidity and mortality in Nigeria, and G6PD deficiency has been implicated as a leading cause of severe hyperbilirubinemia and acute bilirubin encephalopathy.[1–4] A previous study in Nigeria identified G6PD deficiency in up to 62% of infants admitted from home with severe neonatal jaundice and kernicterus.[4] In the current study, the

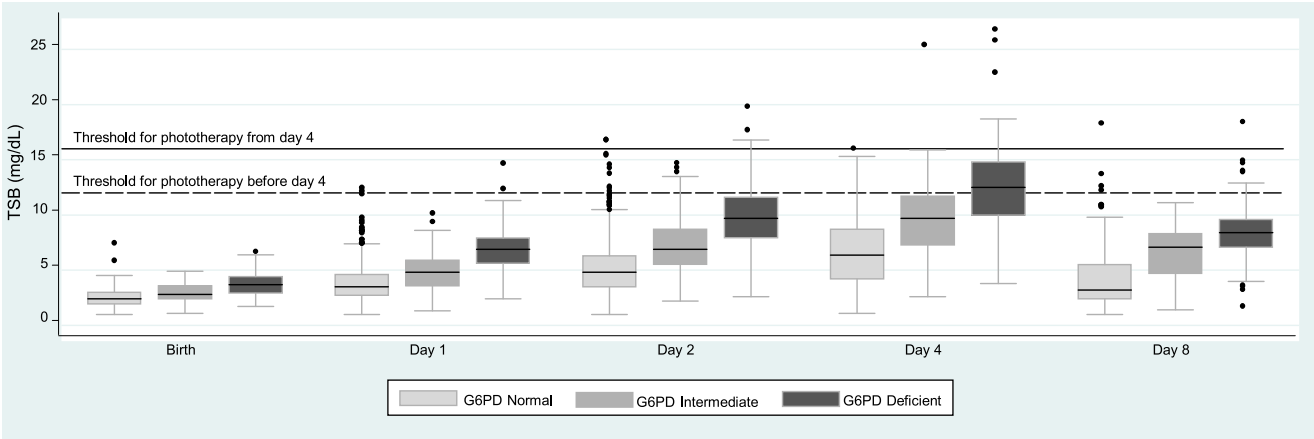

FIGURE 1
Trend of TSB (mg/dL) by G6PD status in the first week after delivery.

TABLE 3 The Distribution of Mean of Hematocrits of the Infants in Relation to G6PD Status

Time	Hematocrit (%)						P^a
	G6PD Deficient (n = 129)		G6PD Intermediate (n = 69)		G6PD Normal (n = 446)		
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
0 h	53.0 (5.0)	42.0–70.0	52.8 (4.8)	41.0–61.0	52.0 (5.5)	33.0–64.0	.11
24 h	52.1 (5.0)	40.0–68.0	51.9 (4.8)	40.0–61.0	51.2 (6.2)	35.0–64.0	.24
48 h	50.3 (4.9)	40.0–64.0	50.3 (7.5)	40.0–60.0	50.4 (5.6)	36.0–64.0	.98
Day 4	48.9 (5.1)	40.0–64.0	49.4 (4.9)	40.0–60.0	49.2 (6.2)	32.0–63.0	.89
Day 8	47.4 (4.9)	34.0–59.0	48.1 (5.1)	33.0–57.0	48.2 (5.1)	34.0–61.0	.32

[a] Analysis of variance.

overall prevalence of G6PD deficiency was ~20% among healthy term and near-term infants, and this was in agreement with the G6PD prevalence figures of 18.2% to 28.7% reported from various earlier studies in Nigeria.[12]

Glucose-6-Phosphate dehydrogenase deficient neonates have long been known to develop severe hyperbilirubinemia when exposed to various icterogenic agents.[5,13] However, significant hyperbilirubinemia has also been observed among G6PD-deficient infants in the absence of exposure to icterogenic agents.[6,14] The current study demonstrated a clear association between G6PD deficiency and hyperbilirubinemia even in the absence of exposure to known icterogenic agents. Increased bilirubin production[15] and deficient bilirubin conjugation coupled with uridine diphosphoglucoronate-glucoronosyl transferase promoter polymorphism (Gilbert syndrome)[16,17] have been suggested as part of the possible explanations for this phenomenon.

From birth, the G6PD-deficient infants in the current study had significantly higher mean TSB values than the G6PD-intermediate infants, who in turn had significantly higher mean TSB than the G6PD-normal infants, and this relationship between the 3 groups was maintained from birth to day 8. The reason for this pattern is not clear, but it may be connected with the larger hematocrit decline that was also observed between day 0 and day 8 among the G6PD-deficient and G6PD-intermediate infants. On the whole, the trend in TSB was similar in the 3 groups, with no significant difference in the age at which the TSB peaked (day 4). However, the mean rate of rise in TSB was significantly higher among the G6PD-deficient and G6PD-intermediate infants, perhaps for similar reasons.

The role of hemolysis in the etiopathogenesis of hyperbilirubinemia among G6PD-deficient infants not exposed to icterogenic agents is controversial. The trend in hematocrits observed in the current study supports the possible role of increased hemolysis among the G6PD-deficient compared with the G6PD-normal infants. This observation supports the findings of earlier studies evaluating the role of hemolysis in the etiology of hyperbilirubinemia in G6PD-deficient neonates.[4,14] Indeed, the day 0 to 8 hematocrit decline, coupled with impaired bilirubin conjugation, may partly explain the higher rate of increase in TSB among the G6PD-deficient and G6PD-intermediate neonates not exposed to known icterogenic agents.[6,16,17] This is even more so, bearing in mind that a small fall in hematocrit may result in a significant rise in bilirubin, as each gram of hemoglobin broken down produces up to 35 mg of bilirubin.[18]

Generally, the prevalence of G6PD deficiency in males reflects the allele frequency of the G6PD gene mutation because the disorder is X linked. Therefore, given that 23.8% of male infants in the current study were G6PD-deficient, it could be extrapolated that

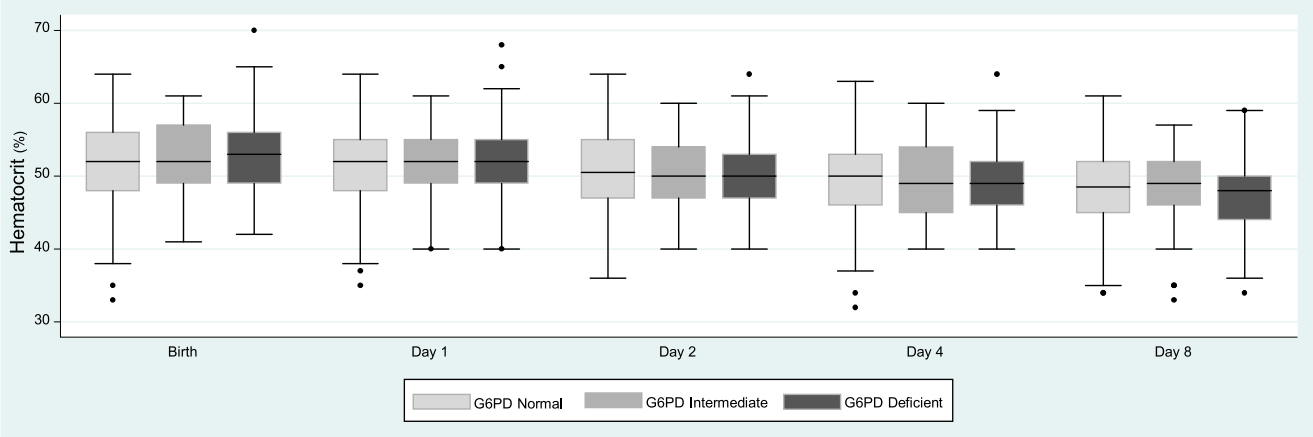

FIGURE 2
Trend of hematocrit (%) by G6PD status in the first week after delivery.

TABLE 4 Clinical Outcomes Based on G6PD Status and Gender

G6PD Status	Gender		Total (n = 644)	P
	Male (n = 353)	Female (n = 291)		
Peak TSB, mean (SD) mg/dL				
Deficient	13.1 (3.8)	13.8 (3.6)	14.1 (9.5)	.31
Intermediate	9.5 (4.6)	10.8 (2.9)	10.2 (3.8)	.17
Normal	6.9 (3.3)	6.9 (3.3)	6.9 (3.4)	.80
Developed significant bilirubinemia, n (%)[a]				
Deficient	53 (63.1)[b]	35 (77.8)[b]	88 (68.2)[b]	.09
Intermediate	6 (19.4)[c]	13 (34.2)[c]	19 (27.5)[c]	.17
Normal	17 (7.1)	16 (7.7)	33 (7.4)	.83
Total	76 (54.3)[d]	64 (45.7)[d]	140 (100.0)	.89
Received phototherapy, n (%)[a]				
Deficient	48 (61.5)[b]	26 (46.4)[b]	74 (55.2)[b]	.99
Intermediate	11 (14.1)[c]	9 (16.1)[c]	20 (14.9)[c]	.28
Normal	19 (24.4)	21 (37.5)	40 (29.9)	.43
Total	78 (58.2)[d]	56 (41.8)[d]	134 (100.0)	.38

[a] Figures in parenthesis are percentages of total in each column

[b] Value for G6DP-deficient infants significantly different from that of G6DP-intermediate infants ($P < .001$).

[c] Value for G6DP-intermediate infants significantly different from that of G6DP-normal infants ($P < .001$).

[d] Figures in parenthesis are percentages of total in that row.

0.238 × 0.238 or 5.6% of female infants were homozygous, and 2 × 0.238 × 0.762, or 36.2%, of female infants were heterozygous. Matching these figures with the prevalence of G6PD deficiency among female subjects in the current study (15.4%), it can be inferred that a number of heterozygous female neonates were G6PD deficient and many more were G6PD intermediate. These findings imply that heterozygous female neonates are also substantially at risk for manifesting G6PD deficiency of variable severity. This is not surprising considering that the residual G6PD enzyme activity associated with the African A– variant (which is the commonest genotype underlying the G6PD-deficient phenotype in Nigeria) varies widely, ranging from 10% to 60%.[19] These findings may therefore be generalizable to other populations in which the African A– variant is prevalent (for example, in other black African countries and among African Americans in the United States).

Globally, phototherapy is the first line of treatment of severe neonatal jaundice, and its use significantly attenuates the peak level of TSB attainable in the newborn period. In the current study, as expected based on the TSB values, a significantly higher proportion of the G6PD-deficient and G6PD-intermediate infants had phototherapy and for a significantly longer duration than their G6PD-normal counterparts. The implication of this is that without the use of phototherapy, the observed difference in TSB levels between the G6PD-deficient and G6PD-normal infants would have been even greater. This prompt deployment of phototherapy may partly explain why the rate of rise of TSB observed in this study is lower than the 0.2 to 0.5 mg/kg/hour commonly cited as clinically relevant. Added to that is the avoidance of exposure of these infants to known icterogenic agents. The current study further revealed that jaundice requiring treatment appeared earlier and persisted to a later age in G6PD-deficient infants. This may partly explain the tendency of untreated hyperbilirubinemia in G6PD-deficient infants to result in acute bilirubin encephalopathy, kernicterus, and neonatal mortality.

Gender on its own did not appear to influence clinical outcomes such as significant bilirubinemia and need for phototherapy because these were found to be comparable between male and female infants in each G6PD stratum. However, the role of genotype, especially among females, needs to be further examined in future studies by correlating the genotype with G6PD phenotype and the clinical outcome in the absence of known icterogen exposure.

Meanwhile, owing to the high prevalence of G6PD deficiency among newborns in Nigeria, it is crucial that a policy of routine G6PD screening at birth is adopted in the country and G6PD-deficient infants are closely monitored for severe hyperbilirubinemia beyond the first week of life to reduce the risk of neonatal jaundice-related morbidity and mortality.[20] There is also a need for additional studies involving G6PD assay and staggered serum bilirubin estimation among Nigerian infants during the first week of life to generate serum bilirubin normograms for G6PD-deficient and G6PD-normal infants to aid in the prediction, diagnosis, and management of clinically significant hyperbilirubinemia in Nigerian neonates.

A limitation of the current study was the reliance on the mothers reported compliance with the advice to avoid exposure of their infants to the known icterogenic agents on the list given to them. Although all the mothers reported compliance, there is still a remote possibility of exposure to as yet unrecognized icterogenic agents in the home environment. This limitation was unavoidable because of the early-discharge policy of the hospital. Mothers were typically discharged from the hospital with their infants on the first or second day after a vaginal delivery, and between the second and fourth day after an uncomplicated caesarean section. It was neither possible nor ethical to keep all the subjects in the hospital for eight days.

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